REMARKS

Claims 1-12 and 92-95 are pending. Claims 4-11 are withdrawn. Claims 13-91 has been previously canceled. No new matter has been added.

Priority

The Examiner states at page 3 of the Office Action that provisional applications 60/423,805 and 60/493,874 do not disclose SDF-1 and fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of the instant application. As such, the Examiner has established the priority date of the instant application as the filing date, i.e. November 5, 2003. Applicant respectfully disagree.

Applicants submit that SDF-1 is disclosed within the Detailed Description of U.S.S.N. 60/493,874 (filed August 8, 2003) at page 13, line 22. Furthermore, SDF-1 is recited within this provisional application as one species of a genus of exogenous growth factor and or cytokine that is expressed by rMSCs of the invention. In the larger context, at page 13, SDF-1 is recited as a spieces of the genus of exogenous polypeptides, that are expressed in MCSs of the invention, by introduction of exogenous nucleic acid molecules that encode for these exogenous polypeptides. Example 3 of this provisional application provides all of the general methods that the skilled artisan would require to be able to make and use the invention. Following the guidance of Example 3, one of ordinary skill in the art would know how to generate and introduce a construct containing a SDF-1 gene into a rMSC. The 60/493,874 provisional application also provides guidance regarding the transplantation of rMSCs into a host and evaluation of the effectiveness of that transplantation. Example 2 demonstrates how to generate constructs to introducing exogenous genes into MSCs, how to insert exogenous genes into MSCs, and how to evaluate the success of these procedures using Akt as one species of the genus of exogenous polypeptides. As such, Applicants submit that U.S.S.N. 60/493,874 satisfies the requirements of the first paragraph of 35 U.S.C. 112 with respect to SDF-1 because the specification provides sufficient description and guidance to enable the ordinarily skilled artisan to make and use the invention by demonstrating the invention for at least one species of a genus to which SDF-1 belongs. Moreover, Applicants contend that the claim for the benefit of a prior-filed application under 35 U.S.C. § 120 is proper with respect to provisional application 60/493,874.

Applicants assume in the foregoing arguments, that the benefit claim of priority to U.S.S.N. 60/493,874, filed August 8, 2003, has been granted.

Claim Rejections under 35 U.S.C. § 103

Claims 1-3, 96, and 97 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over Matsui et al. (Circulation 2001; 104:330-5), in view of Greenberger et al. (US 5,993,801), and Shake et al. (Ann Thorac Surg 2002; 73:1919-26), and as evidenced by Matsui et al. (Circulation 1999; 100:2373-9). Applicants traverse.

The Examiner's grounds for rejection are as follows:

> it would have been obvious to one or ordinary skill in the art at the time the invention was made to modify the methods taught by *Matsui et al,* with that of *Greenberger* and *Shake et al*, by administering mesenchymal stem cells expressing an exogenous Akt gene in place of the adenoviral vector with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because not only MSC was a well known transgene carrier but also have the potential to directly repair/regenerating cardiomyocytes. Given that each of the cited references teaches an agent that is effective in cardia tissue repair/regeneration and in gene transfer, one would have had a reasonable expectation of success combining akt nucleic acid and mesenchymal stem cells. Thus the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Matsui et al. (2001) fail to teach all required elements of the pending claims. As stated by the Examiner, Matsui et al. do not teach administering a mesechymal stem cell genetically modified to express the Akt gene. Instead, Matsui directly injects into heart tissue an adenoviral vector containing the Akt gene.

Greenberger was cited by the Examiner for description of the use of mesenchymal stem cells as carriers to deliver an exogenous gene to a patient in need of such a transgene. In Greenberger, the gene is an enzyme that is expressed and secreted in the bloodstream by stromal cells transfected with an exogenous gene. The purpose for doing so is to correct a genetic deficiency, i.e., the gene to be transfected is a gene that is deficient in the subject to be treated. For example, the transgene encodes Factor VIII-C to treat a bleeding disorder, Hemophilia A, characterized by a deficiency of this factor.

Shake et al. was cited by the Examiner to establish that it was well known in the art that mesenchymal stem cells are capable of differentiating into cardiomyocytes, and thus could be

used to repairing damaging cardiomyocytes. Shake et al. report that mesenchymal cells engraft into host myocardium when implanted by direct injection.

Matsui et al., (1999) show that adenoviral gene transfer of PI3 kinase and Akt inhibits apoptosis of hypoxic cardiomyocytes *in vitro*.

The combination of references fails to teach all of the elements of the claims. The primary Matsui reference not only describes a method of directly injecting the Akt gene in a viral vector into the heart but also speaks to the mechanism of improved function of surviving cardiomyocytes. This teaching steers the skilled artisan away from the cells required by the claims. For example, on page 332, col. 2, the authors state "we examined the functional effects of Akt activation in surviving cardiomyocytes subjected to transient hypoxia in vitro. Expression of myr-Akt blocked hypoxia-induced myocyte dysfunction, preserving contractile function (dL/dt) and calcium handling....". On page 333, col. 1, the authors go on to say "Akt activation induced increased sarcolemmal expression of Glut-4, which was even more marked after ischemia (Figure 6, top). Sarcolemmal translocation of Glut-4, which can serve as a direct target of Akt in some settings is a well-documented effect of Akt activation in muscle." Correspondingly, Akt activation enhanced cardiomyocyte glucose uptake in vitro to levels seen with insulin stimulation (Figure 6)." (citations omitted). The authors' concluding remarks state: "These data establish an important role for Akt in the adult heart in vivo...." (page 333, col. 2) and "Akt is an important modulator of function in cardiomyocytes..." (page 334, col.1). Emphasis added in each quote.

The overriding message from this publication is that the effect of Akt is due to its expression and action in cardiomyocytes of an adult heart. No stem cells of any sort are described or discussed. Given that Akt works directly in cardiomyocytes, there would be no reasonable expectation of success by putting Akt in a mesenchymal cell and delivering the Akt-MSCs to the myocardium, because the Akt would be inaccessible to the cardiomyocytes (in which cells it must act to confer a benefit). There is no reason why a skilled artisan would make Akt-MSCs and deliver those cells to the heart if (as Matsui teaches) the role of Akt is inside a mature adult cardiomyocyte.

As was discussed above, Greenberger use bone marrow stromal cells as a delivery vehicle for transgenes. The class of transgenes to be delivered as those that encode proteins that are secreted into the bloodstream to replace a factor that is missing in the patient to be treated.

Contrary to the Examiner's position, this paper does not stand for a teaching that stem cells are used to deliver any exogenous gene. The role of the cells in Greenberger is to "produce and secrete" and the exemplary transgenes include Factor VIII and TGFα, each of which are secreted. The Akt gene is neither described nor suggested by this reference. Based on the combined teaching of these two references, one of skill in the art would not have any reason to put an Akt gene into a mesenchymal stem cell, because Akt is not a secreted factor.

Finally, the Shake et al. reference was combined with Matsui (2001 and 1999) and Greenberger to support the position that the skilled artisan would be motivated to make Akt-MSCs. Shake et al. report implantation of autologous mesenchymal stem cells, their engraftment in host myocardium, and possible beneficial effects. However, when asked "What do you think about pretreatment of such cells before implantation?", Dr. Shake replied, "Well, we have seen that we do not need to pretreat." (page 1926, col. 1, of Shake et al). Thus, rather than supporting a pretreatment, e.g., introduction of an exogenous gene, this paper teaches away from any sort of pretreatment of mesenchymal stem cells prior to implantation.

The rejection for obviousness based on this combination of references cannot stand. Withdrawal of the rejection is respectfully requested.

Claims 12 and 92, which further require and exogenous gene encoding a growth factor or cytokine, were rejected for obviousness over the same combination of reference and in further view of Palasis et al. Here, the Examiner's position is that Palasis et al. "remedy the deficiency by a showing that it was well known in the art many therapeutic genes such as growth factors could be delivered locally to ischemic myocardium to promote recover from injury". However, the Palasis reference fails to provide the claim elements missing from the combined teaching described above. With or without Palasis, the combination of cited references teaches away from making and using Akt-MSCs as claimed.

Claims 12, and 92-95 were newly rejected for obviousness. The rejection is based on Matsui(2001), Greenberger et al., Shake et al., in further view of Penn. The Penn reference was cited for description of cytokines such as G-CSF to "increase stem cell homing to injured cardiac tissue, and enhance recovery" (Office Action at page 8). The Penn reference does not speak to the fundamental claim requirement of mesenchymal stem cells modified to contain an exogenous nucleic acid encoding Akt. Thus, these claims are also non-obvious over the cited art. Reconsideration and withdrawal of the rejection are requested.

CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit, that the pending claims are in condition for allowance. If there are any questions regarding this amendment and/or these remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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